REMARKS

I. Detailed Action

A. Sequence Requirements

The Examiner has made a rejection for the failure of this application to comply with the requirements of 37 CFR § 1.821-§ 1.825. Applicants respectfully submit the submission and compliance of nucleotide and/or amino acid sequences as set forth in 37 CFR § 1.821-§ 1.825 in response to this Office Action.

B. Double Patenting

Claims 1-4, 6-12, and 15 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-7 of U.S. Patent No. 5,869,035. Applicant is herein submitting a terminal disclaimer in compliance with 37 CFR § 1.321(c) which disclaims any term of a patent issuing from this application which would extend beyond the terms of U.S. Patent No. 5,869,035.

Further, Applicant respectfully traverses the Examiner's rejection under 35 U.S.C. § 102(e). Applicants submit that the "conflicting claims" are not identical and are patentably distinct from each other for the below stated reasons. Applicants further submit these arguments will be reiterated under the section of claim rejections of 35 U.S.C. § 102.

The Examiner states that U.S. Patent No. 5,869,035 claims, hereafter referred to as the '035 patent, "recite broad methods of killing tumors comprising delivering to said tumor cells a vector producer cell line with a polynucleotide sequence that comprises a recombinant HSV plasmid vector that expresses α(1,3) galactosyltransferase." In contrast, '035 does not recite the

species of the vector producer cells or the species of the host. Further, as stated in claim 5 of '035 it specifically states "wherein said vector producer cell line does not contain an active murine α1,3 galactosyltransferase gene" (column 32, lines 64-66). In contrast, the claimed invention does specifically state the subject, the murine cells which are LTKOSN.1 vector producing cells wherein the surface glycosylation is α(1,3) galactosyl epitopes (claims 3-6, 10-13). The claims of the present invention are patentably distinct. The Examiner further states that the '035 "specification teaches that mechanism of tumor cell killing is hyperacute rejection mediated largely by complement activation." In contrast, the claimed invention is clearly distinguished from '035. The claimed invention is specific to the treatment of ovarian cancer in humans and provides a method for inducing an immune reaction to attack tumor cells. The claimed method specifically shifts the understanding from '035 to the present invention whereby murine VPC xenografts would provide production of retroviral vectors within solid tumors and efficiently transfer the HSVtk gene and the bystander effect would enhance the effect allowing for a small portion of the tumor to be transduced while the entire tumor could be destroyed (pages 16-17, specification). In addition, '035 was incorporated by reference to the present invention allowing for inclusion of the method of infusing cells which transfect the tumor cells with a gene that the immune system will respond to, for example, one which creates α(1,3) galactosyl epitopes in a human system (page 14, specification). "The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed." MPEP § 2163.07(b).

Applicants respectfully submit that the case law stated by the Examiner does establish anticipation for composition, product and apparatus claims but not for process (method) claims. See MPEP § 2112.02. Applicants assert that although similar structures are identified the

disclosure is inherently different and "anticipation focuses on whether a claim reads on the product or process a prior art reference discloses, not on what the reference broadly "teaches". Kalman v. Kimberly-Clark Corp., 713 F.2d 760 (Fed. Cir. 1983). Further, "for a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 677 (Fed. Cir. 1988). The claims in the present invention are clearly different from, and therefore not anticipated by the teachings of '035.

Therefore, in light of the above remarks, Applicants submit that the present invention is clearly distinguished from and not anticipated by '035 and that the claims are in proper form for allowance and respectfully request reconsideration and withdrawal of the obviousness-type double patenting and 35 U.S.C. § 102(e) rejections.

II. Claim Rejections – 35 U.S.C. § 112, First Paragraph

Claims 1-16 and 18 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states that the specification "does not reasonably provide enablement for methods of treating tumors or methods of treating tumors comprising inducing hyperacute rejection wherein the method steps comprise the injection or infusion of any and all xenogeneic cells." The Examiner also states the specification does not provide an enabling disclosure "for the induction of treatment of tumors by inducing hyperacute rejection through any means or by the injection/infusion of any type of xenogeneic cells to any type of host mammal."

Applicants respectfully traverse this rejection. The test for enablement under § 112, first paragraph, is "whether or not the specification contains a sufficiently explicit disclosure to enable one having ordinary skill in the relevant field to practice the invention claimed therein without the exercise of undue experimentation." Ex Parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. &

Int'f 1986). In Ex Parte Forman, the Board stated that undue experimentation is a "test [that] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed." Id. at 547. The predecessor to the Federal Circuit has stated:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995), citing In re Marzocchi, 439 F.2d 220, 223 (C.C.P.A. 1971) (emphasis supplied).

Applicants submit the specification does reasonably provide methods of treating tumors (pages 17-19). The specification states that the "process of hyperacute rejection associated with the administration of murine VPC" has an adverse effect on the intraperitoneal tumor and that "one of ordinary skill would be able to determine methods of presenting xenogenic cells to the body in order to induce hyperacute rejection and bystander effect" (pages 18-19). Further, it is disclosed that "any xenogeneic cells which will activate the hyperacute rejection will be effective" in the claimed invention and that one of ordinary skill would be able to determine which cells other than murine cells will be safe and effective (pages 18-19). The current understanding has been that HSVtk and ganciclovir gene therapy is efficacious for the treatment of solid tumors in adults. The claimed invention shifts this understanding to suggest that murine

VPC xenografts will provide production of retroviral vectors within solid tumors and efficiently transfer the HSVtk gene thereby sensitizing solid tumors to GCV and permit a bystander effect caused by metabolic cooperation allowing for a small portion of the tumor to be transduced with HSVtk while permitting the entire tumor to be destroyed. Applicants further submit that it is known in the art that α(1,3) galactosyltransferase gene is not active in humans due to the presence of two base pair frameshift mutations (page 9). However, the transfer of the porcine α(1,3) galactosyltransferase adds α(1,3) galactosyl epitopes to human fibroblasts results in sensitivity to Ab and complement destruction. Applicants have discovered that retroviral transduction of human tumor cells with the α(1,3) galactosyltransferase gene results in its expression thereby allowing a hyperacute rejection that presents a strong intraperitoneal inflammatory response, which through an innocent bystander mechanism, destroys ovarian cancer cells. The claimed invention teaches that there are two mechanisms of cell killing; one is HSVtk/GCV mediated killing and the second is hyperacute rejection associated with tumor killing (page 18). Applicants respectfully submit that the claims in conjunction with the specification do provide guidance to persons skilled in the art to readily ascertain and perform the claimed invention.

The Examiner also states that the specification "fails to provide guidance for the expression of any genes other than HSVtk and α(1,3) galactosyltransferase in the xenogeneic cells of the instant invention or teach that the expression of any other gene in the xenogeneic cell results in immune mediated bystander killing of tumors." The Examiner states that "in view of the art recognized unpredictability, the lack of guidance provided by the specification for means of inducing a hyperacute response in any mammal other than the administration of viral producer cells which express HSVtk or α(1,3) galactosyltransferase, the lack of guidance concerning

xenogeneic cell selection and/or vector/gene selection such that the level of induced hyperacute immune responses in vivo correlates with tumor killing, the limitation of the working examples to the administration of murine vector producer cells which produce a retrovirus encoding HSVtk and/or $\alpha(1,3)$ galactosyltransferase, it would have required undue experimentation to practice the scope of the invention as claimed and the skilled artisan would not have predicted success in treating tumors by inducing hyperacute immune responses using any means in the vicinity of the tumor."

Applicants respectfully traverse this rejection. Applicants submit it is not required for there to be a working example of each component of the invention but rather "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." In re Wright, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). In addition, "how a teaching is set forth, by specific example or broad terminology, is not important." In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue." In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). Thus, "any conclusion of non-enablement must be based on the evidence as a whole." Id. at 740. Applicants respectfully submit that the specification is enabled to one skilled in the art for the claims presented and does not require undue experimentation. Further Ross et al. does not disclose how to make or use the claimed invention for one skilled in the art. The cited reference also does not disclose the claimed invention and although it implies "unpredictability" it does so at the time of the article being written and not the date of the claimed invention whereby "one skilled in the art can readily anticipate the effect of change within the subject matter." MPEP §

2164.03. In addition, Orkin et al. also discussed the "difficulties" with gene therapy but this does not prove that the claimed invention is not enabled at the time of filing. Orkin et al. also discusses other methods of indirect gene therapy however this does not substantiate that those skilled in the art could not perform the claimed problem to be solved as of the filing date. Finally, Verma et al. states what is already known in the art as of the filing date of the present invention, that gene therapy is an "experimental strategy for patients" (see specification, page 1). Applicants therefore respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

III. Claim Rejections – 35 U.S.C. § 112, Second Paragraph

Claims 6-8 and 15-16 were rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps. The Examiner states "the method fails to recite any particular step which results in the induction of hyperacute rejection." Applicants submit that they have now amended the claims. Claim 6 has now been amended to further define the steps that result in the induction of a hyperacute rejection. Applicants submit that claims 7 and 8 are now allowable with the amendment of claim 6. Claim 16 has been amended to make it more definite. However, Applicants respectfully traverse this rejection and submit that these claims are clear as to the metes and bounds of the invention. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

IV. Claim Rejections – 35 U.S.C. § 102

35 U.S.C. § 102(e)

Claims 1-4, 6-12, and 15 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,869,035. Applicants respectfully submit that the terminal disclaimer that has

been submitted in conjunction with the arguments stated previously in section I. Detailed Action, allow for this ground of rejection to be withdrawn.

Claims 1, 3-4, 6, 9-12, and 15-16 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,045,789, hereafter referred to as Culver et al. The Examiner states that Culver et al. "teaches the treatment of tumors comprising the administration of xenogeneic murine retrovirus producing cells directly to a tumor in a subject which includes humans wherein the murine cells produce a retrovirus which encodes HSVtk and IL-2 such that an immune response is generated against the tumor and that tumor cells are also killed directly by HSVtk/ganciclovir or indirectly by innocent bystander effect" thereby Culver et al. anticipates the claimed invention.

Applicants respectfully traverse this rejection. It is axiomatic that for a proper anticipation rejection, the cited reference must contain each and every element of the claimed invention. Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopedics, Inc., 976 F.2d 1559 (Fed. Cir. 1992). Further, the absence from a prior art reference of any claimed element negates anticipation. Id. The present invention is directed to a method of treating tumors in the human subject comprising adding an amount of xenogeneic cells to the peritoneal around or within the tumor which activates hyperacute rejection of the cells in an immune reaction to the tumor, and methods of treating tumors by inducing a hyperacute rejection in and/or in the vicinity of the tumor. Further, Applicants claim the method wherein hyperacute rejection comprises infusion or xenotransplantation of xenogeneic cells which have a surface glycosylation pattern that includes $\alpha(1,3)$ galactosyl epitopes, and wherein said tumors are solid tumors selected from a group which includes ovarian carcinomas. In comparison, Culver et al. does not teach that the murine cells express $\alpha(1,3)$ galactosyl epitopes. Applicants respectfully submit that it is not an

"inherent" property of murine cells to utilize α(1,3) galactosyltransferase without using the claimed invention and its incorporated references. In addition, the cited reference claims immunotherapy employing single cytokine molecules. This does not teach or suggest the use of HSVtk gene activation of GCV leading to a bystander effect that accounts for anti-tumor responses. The claimed invention's discovery of vector producer cells as delivery vehicles is not taught by the cited reference. Furthermore, Culver et al. does not teach to one skilled in the art how to induce an immune effect mediated by the activation of hyperacute rejection against non-primate cells that are infused to produce murine retroviral vectors *in situ*. The claimed invention shifts the understanding at the time of Culver et al. Instead of HSVtk and ganciclovir gene therapy treatment for solid tumors in adults, the claimed invention teaches that murine VPC xenografts will provide the production of retroviral vectors and efficiently transfer the HSVtk gene. The implantation of VPC is superior to implanting HSVtk pre-transduced cells alone to increase the delivery of the HSVtk gene. Furthermore, the claimed invention teaches a high level gene transfer which is opposite of the cited reference, where there is less than 50% pretransduced cells. Furthermore, Culver et al. is also using a cytotoxic drug in order to determine, *ex vivo*, that the tumor cells exhibit a bystander effect, the present invention does not (claim 1, Culver et al.).

Applicants submit that the case law stated by the Examiner does establish anticipation for composition, product and apparatus claims but not for process (method) claims. See MPEP § 2112.02. Applicants assert that although similar structures are identified the disclosure is inherently different and "anticipation focuses on whether a claim reads on the product or process a prior art reference discloses, not on what the reference broadly "teaches". Kalman v. Kimberly-Clark Corp., 713 F.2d 760 (Fed. Cir. 1983). Further, "for a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a

single reference." Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 677 (Fed. Cir. 1988). The claims in the present invention are clearly different from, and therefore not anticipated by the teachings of Culver et al. Applicants further respectfully submit that it would not have been obvious to treat humans with LTKOSN.1 VPC and GCV or by an induced immune effect mediated by the activation of hyperacute rejection against non-primate cells that are infused to produce murine retroviral vectors *in situ*. The innocent bystander effect that then occurs which induces the destruction of adjacent cancer cells and stimulates anti-tumor immunity would also not have been obvious.

Therefore, in light of the above remarks, Applicants submit that the present invention is clearly distinguished from and not anticipated by the cited references and that the claims are in proper form for allowance and respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(e).

35 U.S.C. § 102(a)

Claims 1-4, 6-12, and 15 were rejected under 35 U.S.C § 102(a) as anticipated by Klatzmann et al. (1998) Human Gene Therapy, Vol. 9, 2585-2594. The Examiner states that Klatzmann et al. teaches the treatment of melanoma tumors in humans by direct intratumoral injection of a xenogeneic murine retroviral producing cell line that produces a retrovirus encoding HSV-TK followed by the administration of ganciclovir (Klatzmann et al., page 2585). The Examiner states that "by teaching all the limitations of the instant methods, Klatzmann et al. anticipates the invention as claimed."

Applicants respectfully traverse this rejection. Anticipation focuses on whether a claim reads on the product or process a prior art reference discloses, not in what the reference broadly "teaches." Kalman v. Kimberly-Clark Corp., 713 F.2d 760 (Fed. Cir. 1983). In light of the

above, Applicants respectfully submit that the present invention is clearly distinguished from, and therefore, not anticipated by Klatzmann et al. Applicants respectfully submit that the cited reference does not necessarily possess the characteristics of the claimed product. In re Best, 195 U.S.P.Q. 430, 433 (C.C.P.A. 1977). Although Klatzmann et al. teaches the treatment of tumors by direct intratumoral injection. It does not teach or suggest that the murine retroviral producer cells express α(1,3) galactosyl epitopes which is an inherent property of murine cells that they utilize α(1,3) galactosyltransferase in protein glycosylation and that murine proteins contain α(1,3) galactosyl epitopes. Further, Klatzmann et al. does not teach the administration of the xenogeneic retroviral producer cells generating an immune response against the tumor cells themselves or that the immune response causes an innocent bystander response resulting from the hyperacute rejection of the xenogeneic cells. The claimed invention teaches the addition of the α(1,3) galactosyltransferase to a retrovirus encoding HSVtk, which the cited reference does not teach or suggest.

In light of the above, Applicants submit that the present invention is clearly distinguished from and, therefore, not anticipated by Klatzmann et al. Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(a).

V. Claim Rejections – 35 U.S.C. § 103(a)

Claims 1, 3-6, and 9-17 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,045,789, referred to as Culver et al., in view of Link et al. (1998) Human Gene Ther., Vol., 9(1), 115-134, and further in view of Link et al. (1998) Anticancer Res., Vol. 18, 2301-2308, hereafter referred to as Levy et al. The Examiner states that "based on the teachings of Culver et al., that many different retroviral vectors encoding HSVtk can be used to treat tumors using the disclosed methodology, and the successful expression of HSVtk in cells

using the LTKOSN.1 vector taught by Link et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to use the LTKOSN.1 vector taught by Link in the method of treating tumors taught by Culver et al., and the skilled artisan would have had a reasonable expectation of success in transducing tumor cells with the LTKOSN.1 vector."

Applicants respectfully traverse this rejection. It is in error to reconstruct the patentees' claimed invention from the prior art reference by using the patentees' claims as a blueprint. When prior art references require selective combination to render obvious the subsequent invention, there must be some reason for the combination other than the hindsight obtained from the invention itself. It is critical to understand the particular results the new combination achieved. See Interconnect Planning Corp. v. Feil, 774 F.2d 1132 (Fed. Cir. 1985). As Applicants have discussed in the context of the 35 U.S.C. § 102(e) rejection above, the present invention is clearly distinguished from the teachings of Culver et al. Neither Culver et al. nor Link et al. teaches the addition of the gene for α(1,3) galactosyltransferase to a retrovirus encoding HSVtk. It is important to note that murine cells express a surface glycosylation pattern that is not present on human cells. The murine α(1,3) galactosyltransferase enzyme adds α(1,3) galactosyl epitopes onto glycoproteins and glycolipids. Pre-existing human antibody combine these epitopes and fixed compliment resulting in the direct lysis of the murine cells. An innocent bystander effect then occurs which induces the destruction of adjacent cancer cells and stimulates anti-tumor immunity. HSVtk activation of GCV alone only has a minor contribution to the observed anti-tumor responses of the claimed invention but nonetheless is what is solely being stated in the cited references. Finally, while Culver et al. teaches IL-2 inclusion in a retrovirus is useful for treating solid tumors including ovarian tumors, the cited references do not teach nor suggest the production of murine retroviral vectors with the addition of the gene α(1,3)

galactosyltransferase that are utilized in inducing an immune effect mediated by the activation of hyperacute rejection of a retrovirus encoding HSVtk.

In light of the above, the present invention is clearly distinguished and non-obvious over Culver et al., in view of Link et al., and further in view of Levy et al. Applicants respectfully request reconsideration of withdrawal of the objection under 35 U.S.C. § 103(a).

VI. Conclusion

In light of the above remarks, Applicants respectfully assert that claims 1-18 are now in condition for allowance. Applicants respectfully request reconsideration and withdrawal of the above rejections.

No fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Reconsideration and allowance is respectfully requested.

Respectfully submitted,

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AMENDMENT — VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

The paragraph at page 29, beginning at line 11, has been amended as follows:

MLVENV-F (5'-ACCTGGAGAGTCACCAACC-3') SEQ ID NO: 1 and MLVENV-R (5'-TACTTTGGAGAGGTCGTAGC-3') SEQ ID NO: 2 were designed to amplify a 411 bp fragment of the env gene. The PCR reaction was 3 min. at 94°C, followed by 30 cycles of 94°C for 20 seconds, 68°C for 1 minute, and 72°C for 1 minute, with a final extension of 10 minutes at 72°C. The reaction mix was 500 ng of genomic DNA (sample), 25 pmoles of each primer, 1X PCR buffer, 0.2 mM dNTPs, 1.25 MM $MgCl_2$, and 1.25 U Taq. A375 NV cells and a sample containing no genomic DNA were used as negative controls. 100 fg of pPAM3 was used as a positive control for each sample. For the lymphocyte samples, 500 ng of each A375 LTKOSN.1 dilution of genomic DNA ($1x10^{-4}$ and $5x10^{-4}$) was used as additional controls. PCR product from blood lymphocytes and controls were transferred to membrane using a slot blot. The env probe was labeled with (^{32}P)dCTP by the random priming technique (Boehringer Mannheim). The blots were hybridized overnight at 42°C in Hybridisol (Oncor) and washed. No env gene sequence was detected by PCR in PBL samples obtained up to one year after VPC infusion.

The paragraph at page 30, beginning at line 2, has been amended as follows:

PCR primers (JMTKO1 5' TAT AGA CGG TCC TCA CGG GAT 3') SEQ ID NO: 3[;] and JMTKO3 5' TCA TGC TGC CCA TAA GGT AT 3') SEQ ID NO: 4 were designed to amplify a 388 bp fragment of the TK gene. The reaction mix contained 500 ng of genomic DNA sample. A375 NV cells and a sample containing no genomic DNA was used as negative controls. 100 fg of pLTKOSN.1 was used as a positive control for each sample. For the lymphocyte samples, 500 ng of each A375 LTKOSN.1 dilution of genomic DNA (10^{-2}, 10^{-3}, 10^{-4}, and 10^{-5}) was used as additional controls. 500 ng of 10^{-3} and 10^{-4} dilutions of A375 LTKOSN.1 genomic DNA were used as controls for the tumor and peritoneal wash cells. PCR product from blood lymphocytes and controls were transferred to membrane using a slot blot. A TK probe was labeled with (^{32}P)dCTP by the random priming technique (Boehringer Mannheim). PCR products from peritoneal wash and tumor samples were run out on 1.5% TBE gels and Southern transferred onto nylon membrane following manufacturer's instructions. No

HSVtk gene transfer into PBL from patient blood samples up to 3 months after VPC infusion were detected by PCR in any patient.

In the Claims

Please amend claims 3, 6, 12, and 16 as follows:

3. (Amended)

The method of claim 1 wherein the subject is human and the xenogeneic cells have α(1,3) [galactosyl epitopes] galactosyltransferase gene expression.

6. (Amended)

A method of treating tumors comprising inducing a hyperacute rejection to the cells in and/or in the vicinity of the tumor by inducing an intraperitoneal inflammatory response and thereby destroying cancer cells.

12. (Amended)

The method of claim 10 wherein the surface glycosylation pattern not present on human cells is transduced by α(1,3)[galactosyl epitopes] galactosyltransferase displaying α(1,3)galactosyl epitopes on the tumor cells.

16. (Amended)

The method of claim 15 wherein the solid tumors are from the group consisting of ovarian, fallopian, [or] and peritoneal carcinoma.